

REMARKS

Claims 27, 29-32, 34-37, 39-41, 43-50 and 52 are pending in the present application. Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the office action of September 15, 2008, the following actions were taken:

(1) Claims 27, 29, 31, 32, 34-37, 39-41, 43-50, and 52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cserhati and Hollo, *Intl. J. Pharmaceutics* (1994) 08:69-75 (hereinafter "Cserhati") in view of Links and Lewis, *Drugs* (1999) 57(3):293-308 (hereinafter "Links") and further in view of U.S. Patent No. 5,840,714 (hereinafter "Zmitek"); and

(2) Claims 27 and 30 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cserhati in view of Links, Zmitek, and Baumann and Preiss, *J. Chromatography* (2001) 764:173-192 (hereinafter "Baumann").

It is respectfully submitted that the presently pending claims be examined and allowed. Applicants submit that each and every amendment herein, and throughout the prosecution of the present application is fully supported by the specification as originally filed, and that no new matter has been added.

Claim Amendments

Independent claim 27 has been amended to delete the term "optionally" from the third clause in order to assure that the range limitations are required elements of the claim. Applicants assert that no new matter has been presented.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 27, 29, 31, 32, 34-37, 39-41, 43-50, and 52 under 35 U.S.C. 103(a) as being unpatentable over several references.

The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner of the required three criteria for a *prima facie* case of obviousness,

namely 1) that the asserted references as modified or combined must teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined must provide a sufficient likelihood of successfully making the modification or combination, and 3) that the Examiner must identify a reason for the modification or combination asserted. The recent *KSR* Supreme Court case does not change this basic analysis.

With the above background in mind, Applicants submit that the cited references do not support a *prima facie* case for obviousness.

Cserhati in view of Links

The Examiner has reasserted the rejection of claims 27, 29, 31-50, and 52 under 35 U.S.C. § 103 as being unpatentable over Cserhati in view of Links and Zmitek.

The presently amended claims are drawn to a process for the preparation of a low toxicity, stable oxazaphosphorine containing composition which includes mesna, an etherified β -cyclodextrin, and an oxazaphosphorine antineoplastic of a specific structure. The process involves the steps i) of adding the oxazaphosphorine antineoplastic to an aqueous solution of etherified β -cyclodextrin, ii) adding the mesna, either alone or as part of an aqueous solution containing etherified β -cyclodextrin, to the oxazaphosphorine solution, mixing the resultant solution aqueous solution, and adding water the final mixed solution such that the oxazaphosphorine antineoplastic is from 1 mg/ml to about 1000 mg/ml; the etherified β -cyclodextrin is present at a concentration of about 1% to 60% w/v; and the ratio of oxazaphosphorine antineoplastic to mesna is in the range of about 20:1 to about 1:2 on a weight basis.

Before addressing the Examiner's responses to the Applicants previously submitted arguments, Applicants incorporate by reference all of the arguments presented in the previous office action dated June 16, 2008, in particular those arguments relating to the failure of the cited references to teach or suggest all of the elements of the pending claims. Applicants continue to assert that the Examiner has failed to establish a *prima facie* case of obvious.

In the last office action response, Applicants addressed the Examiner's assertion that the last step of the claimed process is a mere "optimization" of the resultant composition. In response to the Applicants' previously submitted arguments, the Examiner cited to *In re Aller*

which states “where the general conditions of a claims are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” First, as presented in the previous office action, Applicants assert that optimization can only be accomplished once a process or method “works” or is known. The present process was not known in the art, nor could one of ordinary skill in the art have been able to perform the present process based on the disclosures of the cited art. The mere knowledge or existence of each of the compositions used in process is insufficient to render the claimed process obvious. Applicants remind the Examiner that the present claims are drawn to a process and not to the resultant composition. Accordingly, Applicants submit that it is not possible to optimize the present process without first having known all of the steps of the process. As the present invention is altogether a different process than that described in the art, optimization of the process cannot itself be deemed obvious.

In support of this, Applicants draw the Examiner’s attention to MPEP §2144.05(II)(b) which reads:

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie* 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

In other words, a parameter which is not already known in the art cannot be optimized. As discussed above, since the resultant composition of the claimed method was not known, it follows that the method of the claimed invention was also not known. (Applicants note that the contrary is not necessarily true, i.e. even if the claimed composition was known, or as asserted by the Examiner, was obvious, the process of making the composition would not necessarily be known since compositions can be made by multiple processes.)

Applicants now look at the specific elements of the pending independent claim with respect to the Examiner’s assertion that the presently pending claims are mere optimizations of what was known in the art. For example, how can the components used in the method to make the resultant composition be mere optimizations of the knowledge in the art, if in fact the resultant composition was not known in the art? How can the presence and the concentrations of the esterified β -cyclodextrin be deemed to be an optimization when it was not known in the art

that the esterified β -cyclodextrin enhances the stability of the oxazaphosphorine and mesna in the aqueous solution? How can the ratio of oxazaphosphorine to mesna be deemed to be a mere optimization if the combination of oxazaphosphorine and mesna was not taught or known by the art?

The Examiner's cited passage from *In re Aller* supports the idea that only "result-effective variables" can be optimized when it states that "where the general conditions of a claims are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." For all of the reasons set forth above, Applicants assert that the present pending claims cannot be held to be a mere optimization of the knowledge in the art, as such a process nor the resultant composition were not previously disclosed in the art. Accordingly, the ranges set forth in the presently pending claims cannot be deemed to be mere optimizations of the art as the variables have not been shown to be "result-effective variables" as set forth in MPEP §2144.05(II)(B) and *In re Antonie*. Therefore, Applicants assert that the Examiner has failed to set forth a *prima facie* case of obvious, and it is respectfully requested that the pending claims be allowed.

Cserhati in view of Links, Zmitek, and Baumann

Claims 27 and 30 were also rejected under 35 U.S.C. § 103 as being unpatentable over Cserhati in view of Links, Zmitek, and Baumann. Baumann is cited as teaching ifosfamide and cyclophosphamide as commonly used oxazaphosphorines in chemotherapy. However, Baumann does not remedy the deficiency of Cserhati, Links, and Zmitek to teach or suggest a stable, parenterally administrable formulation containing both cyclophosphamide or ifosfamide and mesna. The Applicant renews the above arguments with respect to the present combination. As such, the Applicant asserts that the cited references do not support a *prima facie* case for obviousness of pending claims 27 or 30.

The Applicant respectfully asserts the Examiner has not satisfied the requirement for establishing a case of *prima facie* obviousness in any of the above rejections. Therefore, Applicant respectfully submits that the pending claims are allowable, and urges the Examiner to withdraw the rejections.

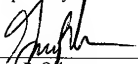
CONCLUSION

In light of the above, Applicant respectfully submits that pending claims 27, 29-32, 34-37, 39-41, 43-50 and 52 are in condition for allowance. Therefore, Applicant requests that the present rejections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after entry of this Amendment, the Examiner is encouraged to call Gary P. Oakeson at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 15th day of January, 2009.

Respectfully submitted,



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